REMARKS

Attached hereto is a marked up version of the changes made to the claims by this amendment. The attachment is captioned "**Version With Markings to Show Changes Made.**"

In response to the objections raised by the Examiner in the May 10, 2001 Office Action, our comments follow. Reconsideration and withdrawal of the rejections of the application are respectfully requested in view of the amendments and remarks herewith, which place the application into condition for allowance.

I. STATUS OF CLAIMS AND FORMAL MATTERS

Claim 65 has been amended; Claims 65-83 are under examination. No new matter is added by this amendment.

It is submitted that the claims, herewith and as originally presented, are patentably distinct over the prior art cited by the Examiner, and that these claims were in full compliance with the requirements of 35 U.S.C. §112. The amendments of and additions to the claims, as presented herein, are not made for purposes of patentability within the meaning of 35 U.S.C. §§§§ 101, 102, 103 or 112. Rather, these amendments and additions are made simply for clarification and to round out the scope of protection to which Applicants are entitled. Support is found throughout the specification and from the pending claims.

It is respectfully submitted that the invention has not been thoroughly appreciated. Accordingly, prior to addressing the matters specifically raised in the Office Action, the following explanation of the invention is offered.

The present invention represents a novel approach for generating positive control reagents that are useful in antibody based diagnostic tests. Antibody based diagnostic tests, such as ELISA assays, are used in the diagnosis of infectious diseases in patients, *inter alia*. These assays are used to detect the presence of antibodies against specific infectious organisms in the sera or plasma of infected patients. A typical assay of this type is illustrated in **Appendix I** hereto. This particular assay detects IgG antibodies directed to a given antigen in test serum. The assay involves exposing the test serum to an immobilized antigen. Antibodies directed against the antigen bind to the immobilized antigen. After washing, a labeled secondary antibody, which recognizes and binds to the constant domain of IgG antibodies is used to detect the bound antibodies.

In diagnostic applications, these assays require the use of reactive sera, e.g. human sera, as a positive control. The positive control reagent is usually serum taken from a patient who is known to

have a positive reaction to the relevant antigen. It is becoming increasingly difficult, however, to source sufficient quantities of human sera or plasma, particularly for diagnostic tests for rarer diseases. Accordingly, synthetic positive control reagents are desirable. A requirement of a synthetic positive control reagent is that it mimics the natural antibodies raised against infectious organisms in human beings. In particular, the positive control reagent must have a binding region which binds to the relevant antigen, and it must have a constant region of a specific immunoglobulin class which can be recognized by class specific anti-human antibodies.

Claims 65-83 of the present application relate to a positive control reagent which can mimic antibodies from reactive human sera. The claimed positive control reagent is in the form of a complex between an antibody derived from a first species (such as a mouse) and a constant domain from an antibody of a second species (i.e., a human). The advantage of this approach is that it allows the ready generation in mice of antibodies which bind to a specific antigen, and subsequent labeling of this antibody with human constant domains. In other words, the murine antibody is labeled with human constant domains so that the murine antibody "looks like" a human antibody to the secondary capture antibody. In order to attach the human constant domain to the mouse antibody, a bifunctional molecule is prepared in which the constant domain is linked to a binding region. The purpose of the binding region is to bind to the mouse antibody and thereby label the mouse antibody with the human domain. These claimed complexes are depicted in Figure 3 of the present application.

II. REQUEST FOR WITHDRAWAL OF RESTRICTION REQUIREMENT

The Examiner and the Commissioner or Director are respectfully petitioned to reconsider the finality of the restriction requirement in light of the following arguments. The Office Action contends that claim 1 is anticipated by the Better *et al* disclosure. Applicants respectfully disagree. Claim 1 is directed toward a chimeric structure comprising at least one C_H domain or an epitope thereof. The specification makes it clear that these constructs are useful as positive control reagents in antibody-based diagnostic tests. An important feature therefore, is that the C_H domain or epitope is capable of being recognized and bound by class-specific capture antibodies. The present inventors have found that individual C_H domains work effectively as recognition sites for class specific capture antibodies. Based on the disclosure of the present specification, a skilled artisan would understand that epitopes within the C_H domain would also perform this function.

Importantly, therefore, the present claims are limited to constructs comprising C_H domains or epitopes thereof.

In contrast, Better *et al* relates to a fusion protein comprising cell targeting domains (eg. antibody fragments) linked to cytotoxic proteins. A range of constructs comprising different ScFV and Fab versions of a humanised anti T-cell antibody is disclosed. One of these constructs comprises two Fd portions of the antibody linked by a 9 amino acid cysteine rich hinge region derived from the C_H2 domain of the same antibody. The sole purpose of this 9 amino acid fragment is to act as a linker between two Fab fragments. There is nothing in the Better *et al* citation that teaches or suggests that this 9 amino acid fragment comprises an epitope of the $C_H2$domain. Attached **Appendix II**, which illustrates the construct depicted in the Better *et al* citation and the construct defined in claim 1 of the present application, is submitted to further clarify our argument. We respectfully submit, therefore, that claim 1 as originally filed is novel over the Better *et al* citation.

In any case, the construct claims that are now under consideration (i.e. claims 65-83) are clearly novel and non-obvious over the Better *et al* citation. It would seem reasonable, therefore, that the Examiner also consider in the present application at least claims 84-89 (which are directed to methods of using the constructs claimed in claims 65-83). See, e.g., MPEP §821.04.

Thus, to any extent necessary, this paper may be considered a Petition to Withdraw, or at least to modify the restriction requirement (e.g., in the event that, after consideration of this paper, the Examiner refuses to do so); and, the fee therefor or any other fee associated herewith, or any overpayment in fees, may be charged or credited to Deposit Account No. 50-0320.

III. THE REJECTION UNDER 35 USC §112, SECOND PARAGRAPH, IS OVERCOME

Claims 65-83 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. This rejection has been obviated by the amendment to claim 65, which does not change or narrow the scope and is without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel as to equivalents. Accordingly, reconsideration and withdrawal of this rejection is earnestly solicited.

IV. THE REJECTIONS UNDER 35 USC §112, FIRST PARAGRAPH, ARE OVERCOME

Claims 72-74 and 80 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to make and/or use the invention. These rejections are respectfully traversed.

Claim 72 is rejected on the basis that "the specification does not teach an antibody which would bind to a histidine rich glycoprotein"; however, claim 72 is directed to a complex in which the human constant domain is linked to a histidine rich glycoprotein. The histidine rich glycoprotein binds directly to the mouse antibody and thus labels the mouse antibody with the human constant domain. The histidine rich glycoprotein corresponds to "Reagent 1" of the bifunctional molecule depicted in Figure 3. Contrary to the comments in the Office Action, therefore, claim 72 is *not* directed to an antibody which would bind to a histidine rich glycoprotein.

Moreover, a person skilled in the art would be able to develop histidine rich glycoprotein binding regions for use in the present invention based on the disclosure in the present application and the knowledge in the art, e.g., the disclosure of the Borza *et al* (1996) and Gorgani *et al* (1997) publications, which are cited and incorporated by reference in the specification at page 8, lines 25-28. A copy of the Abstract of each is attached, with a full copy to follow.

Regarding Claim 73, the Office Action states that "the claimed method could not be applied to an antibody in human serum, as biotin would react indiscriminately with all proteins and antibodies in the serum resulting in the binding of a bifunctional molecule comprising streptavidin to all antibodies and proteins in the sample". The complexes claimed in the present application, however, are isolated complexes that are to be used as positive control reagents in diagnostic assays. They are not to be used in human serum. In the case of the present invention, the biotin-streptavidin system is used in a novel way to label mouse antibodies with human constant domains. This aspect of the invention is depicted in Figure 4 of the present application. A person skilled in the art would be able to readily implement this embodiment of the invention based on the disclosure provided in the specification. A skilled addressee would also understand that the novel complex provides a clear advantage as a positive control reagent for diagnostic antibody assays.

The Office Action rejects claim 80 on the basis that the specification allegedly does not teach a method of detecting the complex if the constant region of the bifunctional molecule comprises a non-naturally occurring combination of C_H domains. This embodiment is described in the specification at page 4, lines 4-10, where it is stated:

"The constant region may consist of a non-naturally occurring combination of C_H domains or epitopes thereof. The constant region may consist of two C_H domains of the same type, for example, two C_H3 domains. Alternatively, the constant region may consist of two different domains. The two different domains, or epitopes thereof, may be derived from antibodies of different classes."

A person skilled in the art would be able to readily generate bifunctional molecules that comprise a combination of two or more C_H domains derived from different antibodies. Further, the Examples describe the cloning of a range of different constant domains and the use of these domains in the generation of bifunctional molecules (see in particular Examples 4 and 5).

The Office Action also states that "one of skill in the art would be subject to undue experimentation in order to screen secondary antibodies in the development of a method for detecting these complexes". However, suitable secondary antibodies could be readily generated by those skilled in the art. Indeed, anti-human antibodies that react with C_H domains derived from IgG, IgA or IgM antibodies were well known and commercially available at the filing date of the present application.

Claims 65 and 80 are rejected on the basis that the specification allegedly does not disclose any epitopes of C_H domains and it cannot be anticipated which fragments of C_H domains will function as an epitope in the context of the bifunctional molecule. However, a person skilled in the art would have been able to determine the location of immunodominant epitopes within C_H domains using techniques that were available at the filing date of the present application. For example, enclosed are copies of the following references, which describe how a person skilled in the art may have gone about the task of mapping these epitopes at the filing date of the present application:

> Jespers *et al* (1997) J Mol Biol 269, 704-718 "Epitope mapping by Negative Selection of Randomized Antigen Libraries displayed on Filamentous phage"
>
> Kuwabara *et al* (1997) Nature Biotechnology 15, 74-78 "Efficient epitope mapping by bacteriophage lambda surface display"

Claim 71 is rejected on the basis that the specification allegedly provides no information as to specific fragments of the mouse Fcγ receptor that would be required to form a complex with the antibody of the first species. It is respectfully submitted that a person would be able to readily generate a fragment of the mouse Fcγ receptor which binds to an antibody based on the publications cited in the specification and incorporated by reference at page 8, lines 22-24.

Based on the above arguments, reconsideration and withdrawal of the rejections under 35 U.S.C. §112, first paragraph, are earnestly solicited.

V. THE REJECTIONS UNDER §102 ARE OVERCOME

Claims 65, 68, 75 and 76 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Yamamoto *et al.* Claims 65, 68, 77 and 78 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Muller *et al.* Claims 65-68 and 75-78 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Koren *et al.* Claims 65, 68, 81 and 82 stand rejected under 35 U.S.C. §102(b) as allegedly anticipated by Zanetti *et al.* These rejections are traversed.

It is respectfully pointed out that a two-prong inquiry must be satisfied in order for a Section 102 rejection to stand. First, the prior art reference must contain all of the elements of the claimed invention. *See Lewmar Marine Inc. v. Barient Inc.,* 3 U.S.P.Q.2d 1766 (Fed. Cir. 1987). Second, the prior art must contain an enabling disclosure. *See Chester v. Miller,* 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See In re Donohue*, 226, U.S.P.Q. 619, 621 (Fed. Cir. 1985).

Applying the law to the instant facts, the references relied upon by the Office Action do not disclose, suggest or enable Applicants' invention. Yamamoto *et al* (1997) relates to a mouse anti-idiotypic IgM antibody, 4C10, bound to human monoclonal antibody L612. Muller *et al* (US 6,057,421) involves mouse anti-idiotypic IgG antibody 2A11, bound to human anti-gp41 antibody. Koren *et al* (US 5,560,911) pertains to complexes of mouse anti-idiotypic antibodies and human anti-pig antibody. And, Zanetti (US 5,583,202) concerns a complex comprising:

> (i) a mouse monoclonal antibody [Sp-3-B4] whose specificity is directed against the $(NANP)_3$ epitope from the parasite *Plasmodium falciparum*; and
>
> (ii) an engineered antibody [y1NANP] to which the *P. falciparum* epitope $(NANP)_3$ has been introduced as a foreign epitope into the CDR3 region of the H chain of the mouse/human chimera $C\gamma_1 61$.

The purpose of the Zanetti complex was to demonstrate that the y1NANP expresses the $(NANP)_3$ epitope in an immunologically accessible form. In this complex, the antibody binding site of the mouse mAb Sp-3-B4 is occupied by the NANP epitope expressed on the CDR3 of y1NANP.

In contrast, in the complex of the present invention, the antibody binding sites are unoccupied. **Appendix III** hereto illustrates the differences between the complex disclosed in Zanetti and the complexes of the present application. Note that the open-ended "comprising" language of claim 65 does not provide for the structure of the Zanetti complex as shown in Appendix III.

Indeed, the complex defined in amended claim 65 is clearly novel over the complexes disclosed in the cited art in that the binding region of the bifunctional molecule is of non-antibody origin. On the contrary, the complexes of the publications cited in the Office Action involve antibodies or parts thereof. The cited references do not teach, suggest, or enable a bifunctional molecule in which the immunoglobulin constant region is not a naturally occurring F_C fragment. Therefore, reconsideration and withdrawal of the Section 102 rejections are believed to be in order and such action is respectfully requested.

VI. THE REJECTIONS UNDER §103 ARE OVERCOME

Claims 69 and 70 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Zanetti, in view of Kronvall and Williamsm Bjorck and Kronvall and Atkinson *et al.* This rejection is respectfully traversed.

The Examiner is respectfully reminded of the case law; namely, that there must be some prior art teaching which would have provided the necessary incentive or motivation for modifying the reference teachings. *In re Laskowski*, 12 U.S.P.Q. 2d 1397, 1399 (Fed. Cir. 1989); *In re Obukowitz*, 27 U.S.P.Q. 2d 1063 (BOPAI 1993). Further, "obvious to try" is not the standard under 35 U.S.C. §103. *In re Fine,* 5 U.S.P.Q. 2d 1596, 1599 (Fed. Cir. 1988). And, as stated by the Court in *In re Fritch*, 23 U.S.P.Q. 2d 1780, 1783-1784 (Fed. Cir. 1992): "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggests the desirability of the modification." Also, the Examiner is respectfully reminded that for the §103 rejection to be proper, both the suggestion of the claimed invention and the expectation of success must be founded in the prior art, and not Applicants' disclosure. *In re Dow*, 5 U.S.P.Q.2d 1529, 1531 (Fed.Cir. 1988).

While it may have been known at the priority date that proteins such as *Streptococcal* protein G, *Staphylococcal* protein A and *Peptostreptococcal magnus* protein L bind to antibodies, the inventive concept of the instant invention resides in the idea of labeling antibodies from a first species (eg. murine antibodies) with constant domains from a second species (eg. human constant

domains). Proteins such as *Streptococcal* protein G, *Staphylococcal* protein A and *Peptostreptococcal magnus* protein L are merely used to facilitate the generation of these complexes. There is nothing in the citations of the Office Action that teaches or suggests the present inventive concept. It is respectfully submitted that the rejection appears to be based entirely on hindsight analysis. Further, none of the citations of the Office Action provide any motivation for a person skilled in the art to produce a complex as defined in claim 69 or 70.

Claim 79 stands rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Zanetti, in view of Mezes *et al.* This rejection is respectfully traversed.

Claim 79 is distinguished and non-obvious over the Zanetti *et al* citation for the reasons discussed above. As stated, a crucial difference between the instant invention and those described by Zanetti and Mezes *et al.* is the unique structure and origin of the chimeric complex. These aspects are not taught or suggested in the documents cited in the art rejections of the Office Action; and, they patentably distinguish the claimed subject matter over the references. Accordingly, it is respectfully submitted that the claims, by their terms, distinguish the claimed subject matter patentably from the prior art.

Reconsideration and withdrawal of the Section 103 rejections are respectfully requested.

CONCLUSION

In view of the remarks and amendments herewith, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are earnestly solicited. The undersigned looks forward to hearing favorably from the Examiner at an early date, and, the Examiner is invited to telephonically contact the undersigned to advance prosecution.

Respectfully submitted,

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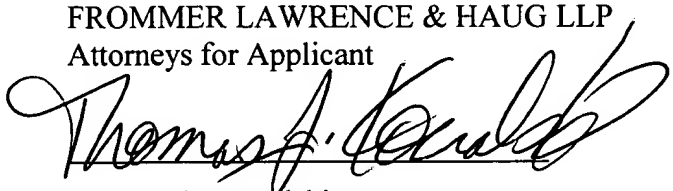
Attorneys for Applicant



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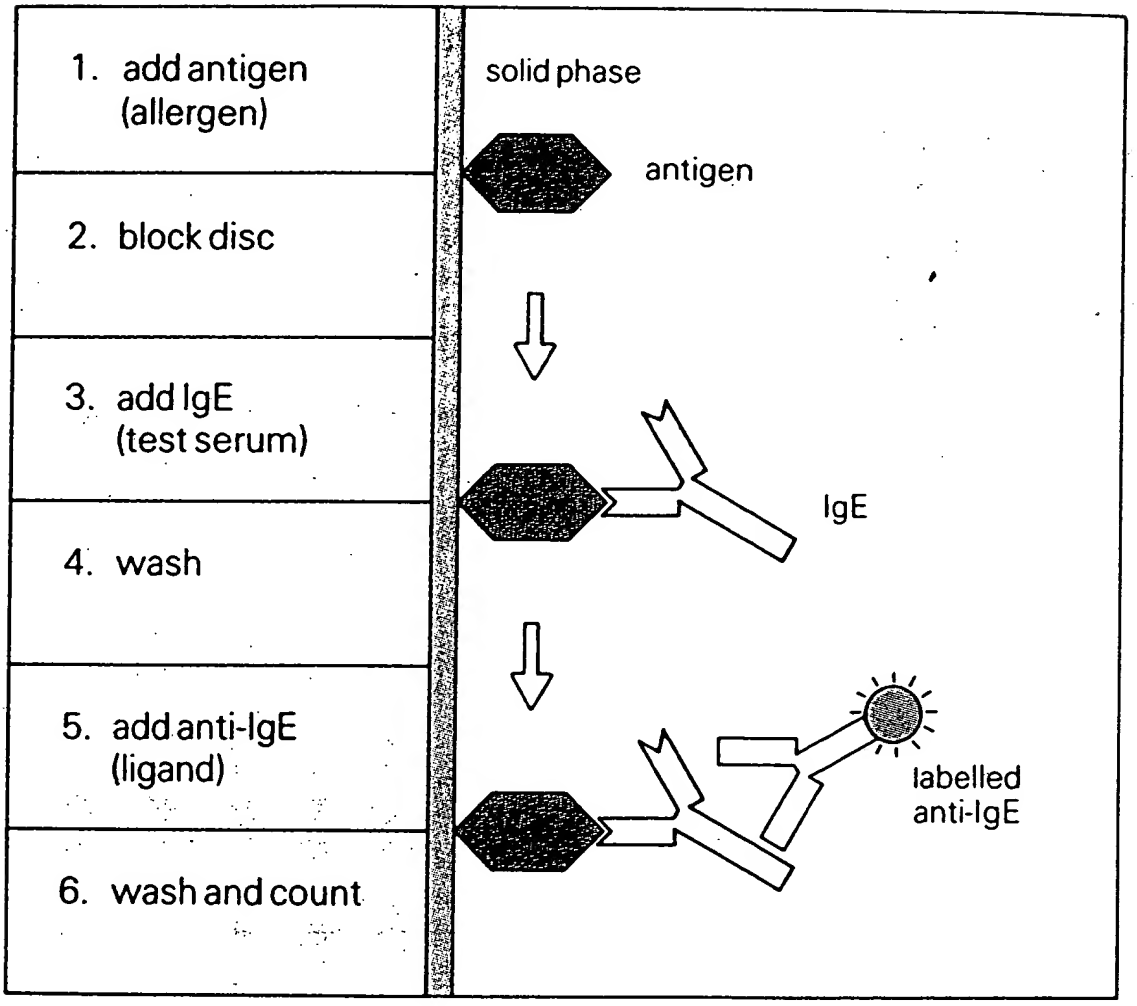
IN THE CLAIMS

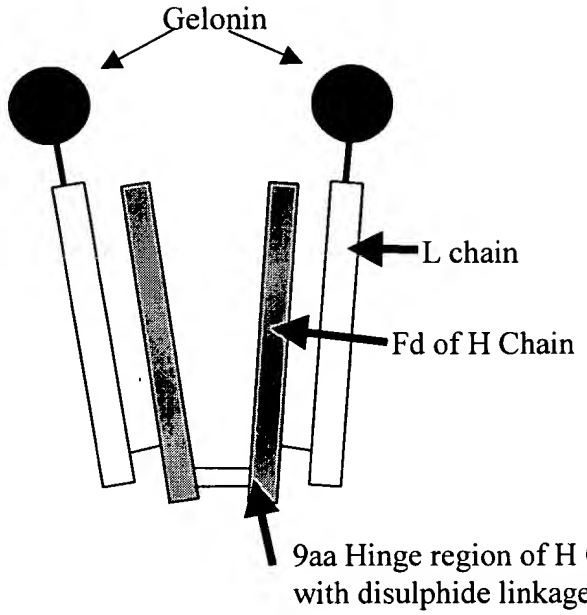
65. A complex formed between (i) an antibody or biologically active fragment thereof derived from a first species and (ii) a bifunctional molecule, the bifunctional molecule comprising a binding region of non-antibody origin which binds to the antibody of the first species or to one or more non-naturally occurring groups provided thereon, and a constant region derived from an antibody of a second species, the constant region comprising at least one C_H domain or an epitope thereof.

Appendix I


1. add antigen (allergen)
2. block disc
3. add IgE (test serum)
4. wash
5. add anti-IgE (ligand)
6. wash and count
solid phase
antigen
IgE
labelled anti-IgE

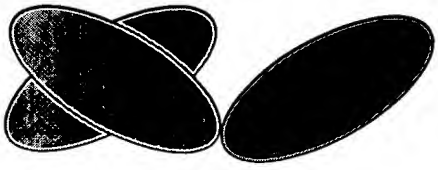
Appendix II

Better *et al.* citation



Claim 1 of the present application

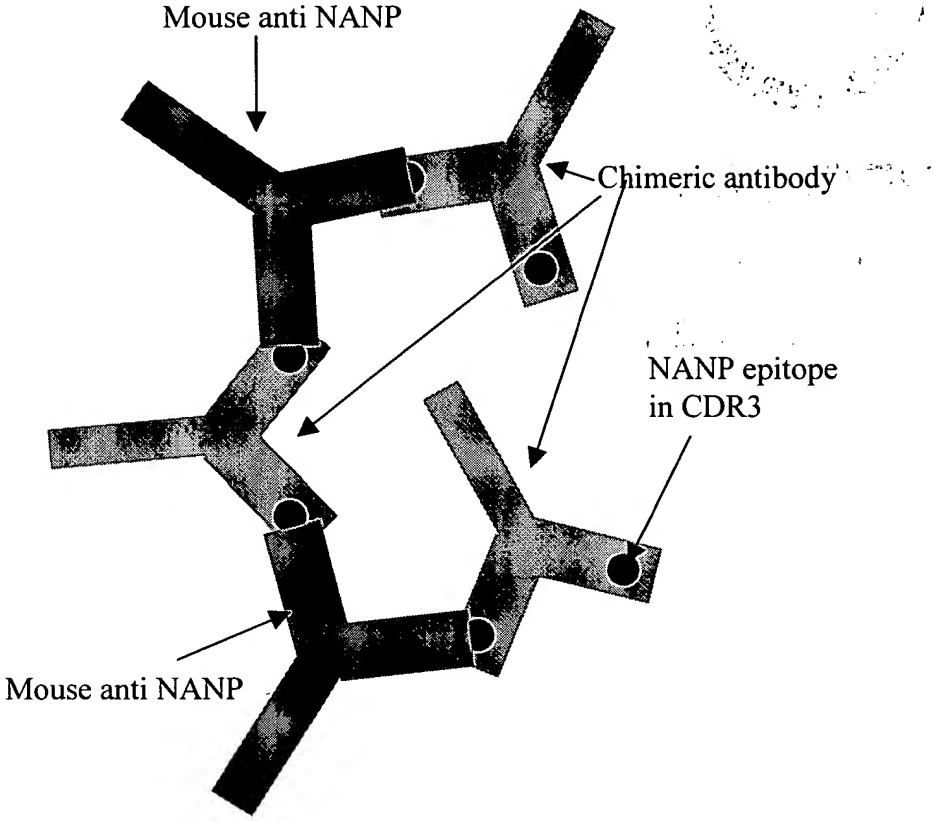
scFv from one species
with activity for antigen



Intact CH domain (or epitope fragment)
CH2, CH3, CH4 from other species

Appendix III

Zanetti Complex



Complex of claims 65, 68, 81 and 82.